Molecules, 2017, vol.22, N12

A novel receptor tyrosine kinase switch promotes gastrointestinal stromal tumor drug resistance

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Abstract

© 2017 by the authors. The fact that most gastrointestinal stromal tumors (GISTs) acquire resistance to imatinib (IM)-based targeted therapy remains the main driving force to identify novel molecular targets that are capable to increase GISTs sensitivity to the current therapeutic regimens. Secondary resistance to IM in GISTs typically occurs due to several mechanisms that include hemi- or homo-zygous deletion of the wild-type KIT allele, overexpression of focal adhesion kinase (FAK) and insulin-like growth factor receptor I (IGF-1R) amplification, BRAF mutation, a RTK switch (loss of c-KIT and gain of c-MET/AXL), etc. We established and characterized the IM-resistant GIST T-1 cell line (GIST T-1R) lacking secondary c-KIT mutations typical for the IM-resistant phenotype. The resistance to IM in GIST T-1R cells was due to RTK switch (loss of c-KIT/gain of FGFR2α). Indeed, we have found that FGFR inhibition reduced cellular viability, induced apoptosis and affected the growth kinetics of the IM-resistant GISTs in vitro. In contrast, IM-naive GIST T-1 parental cells were not susceptible to FGFR inhibition. Importantly, inhibition of FGF-signaling restored the susceptibility to IM in IM-resistant GISTs. Additionally, IM-resistant GISTs were less susceptible to certain chemotherapeutic agents as compared to parental IM-sensitive GIST cells. The chemoresistance in GIST T-1R cells is not due to overexpression of ABC-related transporter proteins and might be the result of upregulation of DNA damage signaling and repair (DDR) genes involved in DNA double-strand break (DSB) repair pathways (e.g., XRCC3, Rad51, etc.). Taken together, the established GIST T-1R cell subline might be used for in vitro and in vivo studies to examine the efficacy and prospective use of FGFR inhibitors for patients with IM-resistant, un-resectable and metastatic forms of GISTs with the type of RTK switch indicated above.

http://dx.doi.org/10.3390/molecules22122152

Keywords

Chemotherapeutic drugs, FGFR2α, Gastrointestinal stromal tumor cells (GISTs), Imatinib (IM), Receptor tyrosine kinase (RTK) inhibitors, Resistance

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